IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Antidepressant Activity of Green-Synthesised Iron Oxide Nanoparticles

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Abstract

Depression is a major global health concern requiring safer and more effective therapeutic interventions. The present study focuses on the green synthesis of iron nanoparticles (FeNPs) using *Curcuma longa* (turmeric) extract and the evaluation of their antidepressant activity. The plant extract, rich in bioactive compounds such as curcumin, was utilized as a reducing and stabilizing agent for nanoparticle synthesis. The synthesized FeNPs were characterized using standard analytical techniques including UV–Visible spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction (XRD) to confirm their formation, size, morphology, and functional groups. The antidepressant activity was evaluated using established in vivo models such as the Forced Swim Test (FST) and Tail Suspension Test (TST). Behavioral parameters including immobility time were recorded and compared with standard antidepressant drugs. The results demonstrated that the green synthesized FeNPs exhibited significant antidepressant-like activity, potentially due to their antioxidant and neuroprotective properties. The synergistic effect of iron nanoparticles and *Curcuma longa* phytoconstituents may contribute to modulation of oxidative stress and neuroinflammation pathways. This study highlights the potential of plant-mediated iron nanoparticles as a novel, eco-friendly, and effective approach for the management of depression, requiring further investigation for clinical applications.

Keywords: Green synthesis; Iron nanoparticles; *Curcuma longa*; Antidepressant activity; Forced swim test; Tail suspension test

1. Introduction

Depression is a prevalent and debilitating mental health disorder characterized by persistent feelings of sadness, low mood, loss of interest, and impaired cognitive and physical functioning. It affects millions of people worldwide and represents a significant global health burden. Despite the availability of various conventional modern drug therapies such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, their use has limitations like delayed onset of action, side effects, and treatment resistance. These limirations leads to exploration of alternative therapeutic approaches like herbal treatments or combinational therapies. In recent years, nanotechnology has emerged as a promising interdisciplinary field with varies applications in medicine, particularly in drug delivery and neurotherapeutics. Nanoparticles exhibit unique physicochemical properties such as high surface area, enhanced reactivity, and improved bioavailability compared to their bulk counterparts. Among various nanomaterials, iron nanoparticles have gained attention due to their biocompatibility, magnetic behavior, and potential to cross the blood–brain barrier, making them suitable candidates for neurological applications.

Conventional methods for nanoparticle synthesis often involve toxic chemicals and energy-intensive processes, which raise environmental and safety concerns. In contrast, green synthesis using plant extracts offers an eco-friendly, cost-effective, and sustainable alternative.It involves use of phytochemicals such as flavonoids, phenolics, and alkaloids present in plant extracts act as reducing and stabilizing agents, facilitating the formation of nanoparticles with enhanced biological activity. These biofunctionalized nanoparticles may exhibit improved pharmacological properties, including antioxidant and neuroprotective effects, which are closely associated with antidepressant activity. Curcuma longa (turmeric) is a well-known medicinal plant widely used in traditional medicine systems due to its rich phytochemical profile, particularly curcumin. Curcumin has been reported to act as a natural reducing and capping agent in nanoparticle synthesis while also imparting significant pharmacological properties including antioxidant, anti-inflammatory, and neuroprotective effects . Previous studies have demonstrated the successful green synthesis of various metal nanoparticles using *Curcuma longa* extracts, highlighting their enhanced biological activities and biomedical potential. Oxidative stress and neuroinflammation are key factors implicated in the pathophysiology of depression. Iron nanoparticles synthesized via green methods may help modulate these pathways, thereby contributing to antidepressant effects. Furthermore, their small size and surface properties may enable better penetration across the blood–brain barrier, enhancing therapeutic efficacy. Additionally, the synergistic effect of iron nanoparticles and *Curcuma longa* phytoconstituents may further enhance therapeutic efficacy.

Therefore, the present study focuses on the green synthesis of iron nanoparticles using *Curcuma longa* extract and the evaluation of their antidepressant activity, aiming to explore a novel, sustainable, and biologically effective approach for the management of depression.

2. Materials and Methods

2.1 Drugs:

Drug (Imipramine) was purchased from standard pharmacy store. Dried rhizome powder of Curcuma longa was collected from authorized ayurvedic store. All the other solvents and chemicals used are of analytical grade.

2.2 Preparation of plant extract

20 grams of plant powder was taken and extracted using 100 ml water by boiling on water bath for 20 minutes and then kept overnight for maximum phytoconstituent extraction. For the synthesis of FeNPs, the aqueous extract was utilized as a reducing and stabilizing agent.

2.3 Green Synthesis of Iron Nanoparticles (FeNPs)

50 ml of Curcuma longa aqueous extract was added to 50 mL of 0.05 mM Ferric Chloride aqueous solution under constant stirring. Intense color change (yellow/brown to dark brown/black) was observed indicating nanoparticle formation. The solution was then sonicated for 60 minutes at room temperature at room temperature and the complete reaction process was carried out.

2.4 Characterization of FeNPs

Several methods, such as Ultraviolet–visible spectroscopy (UV-Vis), Fourier-transform infrared spectroscopy (FTIR), X-ray Diffraction (XRD), were utilized in order to characterize the FeNPs.

2.4.1 UV–Visible-Spectroscopy-Based Analysis

1 mL aliquot of colloidal FeNPs solution in quartz cuvettes was evaluated using UV–visible spectroscopy (SL-218 Elico), using distilled water as a reference and 0.05 mM $FeCl_3$ as a blank, to validate the reduction of the ferric ions in the colloidal solution.

2.4.2 FTIR-Based Analysis

The function groups (biogroups) that were bound on the iron surface and were in- volved in the synthesis of FeNPs were identified using FTIR spectroscopy (FTIR 3110 Jasco). After 72 h of incubation, the FeNPs were isolated by repeated centrifuga- tion (3–4 times) of the reaction mixtures at 10,000 rpm for 15 min. The supernatant was replaced by deionized water and the pellet was stored as powder. After being dried, the FeNPs were put through an FTIR analysis using the potassium bromide pelleting process at a ratio of 1:100.

2.4.3 X-ray Diffraction Analysis (XRD) Analysis

The synthesized iron nanoparticles from aqueous extract of Curcuma longa were subjected to XRD analysis to determine the nature as well as average size of the nanoparticles.

2.5 Evaluation of antidepressant activity

2.5.1 Experimental Animals

Swiss albino mice (18–25 g) of either sex were used for the study. Th e animals were housed and studies were carried out at Animal House of Haffkine's Research Institute, Parel. The animals were housed in colony cages at an ambient temperature of 25+2°C, 12-hr light/dark cycle and 50+5% relative humidity with free access to food and water ad libitum. Food, but not water, was deprived overnight and during the experiment. All the experiments were carried out during the light period (9.00–16.00 hr). Each group consisted of six animals.The institutional animal ethical committee approved the study protocol. Th e dose which was administered to the experimental animals was based on the literature on acute toxicological studies.

2.5.2 Experimental Design

Group-I treated as Vehicle. (Normal Control)
Group-II treated as Depression induced (Shyam Control)
Group-III treated as Standard drug (Imipramine 10mg/kg)
Group-IV treated as Iron Oxide Nanoparticles (200 mg/kg)
Group-V treated as Iron Oxide Nanoparticles (500 mg/kg)

2.5.2.1 Tail suspension test (TST)

The total duration of immobility by the Tail suspension test was measured according to the method of Steru et al[14]. Mice were isolated both acoustically and visually and suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was observed during a 6-min test for animals of all groups. Mice were considered to be immobile when they hung passively and were completely motionless shown in Figure 1a).

2.5.2.2 Forced swim test (FST)

The development of immobility when the mice are placed in an inescapable cylinder filled with water reflects the cessation of persistent escape-directed behaviour. The cylindrical container (diameter 10 cm, height 25 cm) was filled to a 19-cm depth with water at (25$\pm$1°C).The duration of immobility during the 6-min test was scored. Each rat was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water shown in Figure 1b).

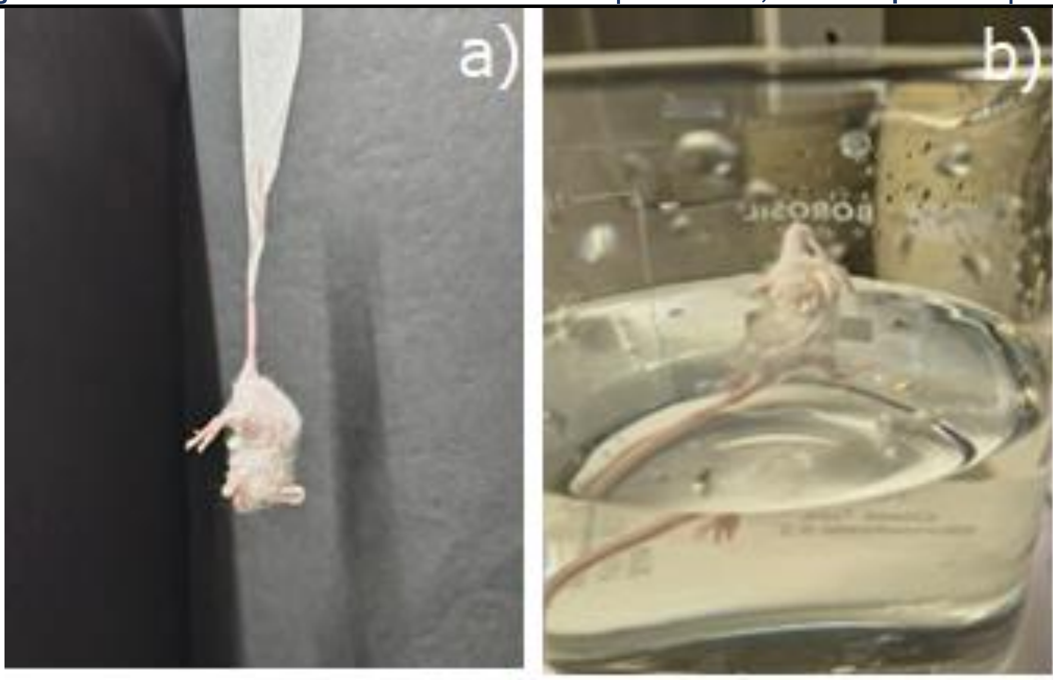

Figure 1 a) Tail suspension test b) forced swim test

3. Results

Figure 2 the UV-Vis spectral measurement of colloidal solution for wavelengths between 200 nm and 700 nm verified the formation of FeNPs. The maximum absorption peak (max) is observed at 290 nm, according to UV-Vis spectral analysis.

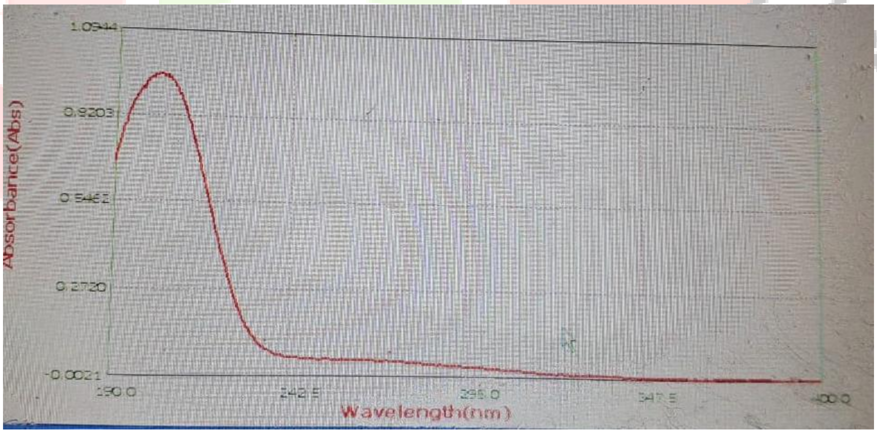

Figure 2 The UV-Vis spectral measurement of colloidal solution of FeNPs

Figure 3 the FTIR spectra revealed presence of some peaks which were responsible for FeNPs formation. However, some functional groups were present in both FTIR spectra of FeNPs, such as alkyl halides, alkynes, aromatics and aliphatic amines, esters, ethers, alcohol, carboxylic acids, and nitro compounds with peaks at 526.57 cm^{-1}, 614.33 cm^{-1}, 815.63 cm^{-1}, 1035.81 cm^{-1}, 1084.34 cm^{-1}, 1132.95 cm^{-1}

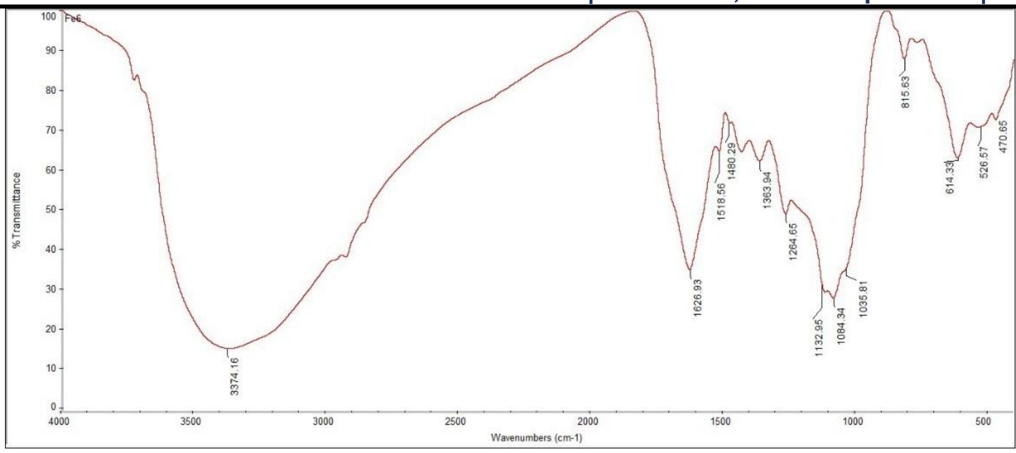

Figure 3 The FTIR spectra Fe_2O_3 NPs

Figure 4, the XRD analysis (Image 5) results showed the sharp peaks at different angles, i.e., 21.87, 29.85, 30.76, 40.40, 43.42, and 46.18. These degrees of angles correspond to the crystalline nature of the material. Hence, it was confirmed that the synthesized iron nanoparticles were crystalline in nature. XRD analysis also confirmed that the synthesized nanoparticles were in nano size with average diameter of 136.43 nm

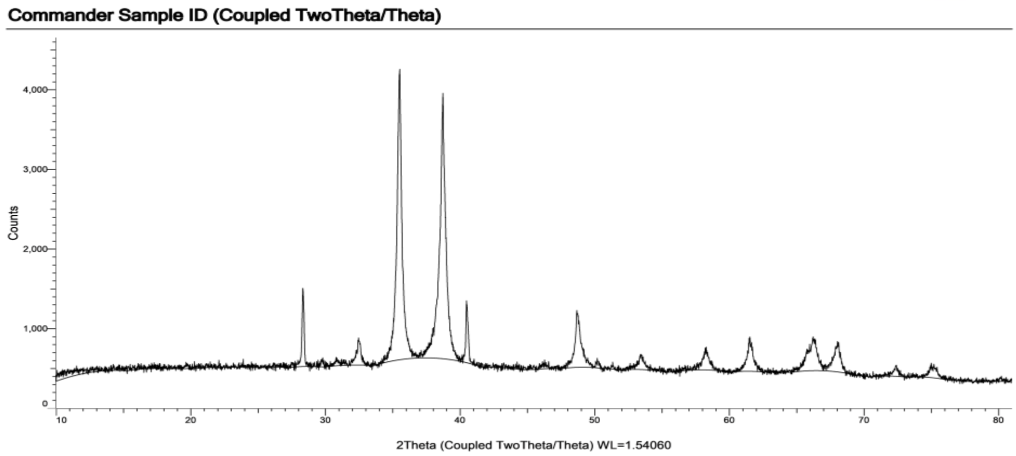

Figure 4 The XRD Image of Fe_2O_3 NPs

The antidepressant effects of FeNPs (200 and 500 mg/kg) were studied by observing the changes in the duration of immobility in the two models, Forced swim test (FST) and Tail suspension test(TST). In both TST and FST, FeNPs 150 and 300 mg/kg,. produced significant reduction in the immobility period when compared with that of control group animals that received only the vehicle and with the standard drug group. The extract (300 mg/kg) was found to be effective and it exhibited activity similar to that of the conventional drug imipramine. The results are tabulated in Table 1 and Table 2.

Tail suspension test:

Table: 1: Effect of FeNps on duration of immobility time in the Tail suspension test

Sr. no	Groups	Treatment	Tail suspension test Duration of immobility(in sec)
1.	Control group	Vehicle (water)	22 $\pm$ 6.17
2.	Shyam Control	Depression Induced	37 $\pm$ 11.006
2.	Standard Dtug	Imipramine (10 mg/kg)	16 $\pm$ 2.25
3.	Test group	FeNps (200 mg/kg)	23 $\pm$ 2.81
4.	Test group	FeNps (500 mg/kg)	16 $\pm$ 1.536

Forced swim test:

Table: 2 Effect of FeNps on duration of immobility time in the Forced swim test

S. no	Groups	Treatment	Forced swim test Duration of immobility(in sec)
1.	Control group	Vehicle (water)	10.3 ± 3.49
2.	Shyam Control	Depression Induced	28 ± 2.43
2.	Standard Dtug	Imipramine (10 mg/kg)	11 ± 1.431
3.	Test group	FeNps (200 mg/kg)	18 ± 2.951
4.	Test group	FeNps (500 mg/kg)	13 ± 1.661

4. Discussion

The present study successfully demonstrated the green synthesis of iron nanoparticles (FeNPs) using *Curcuma longa* extract and evaluated their potential antidepressant activity using validated behavioral models. The findings indicate that the synthesized nanoparticles possess promising antidepressant like effects, which may be attributed to their unique physicochemical properties and the bioactive constituents of the plant extract.

The formation of FeNPs was initially confirmed through UV–Visible spectroscopy, where a characteristic absorption peak was observed at 290 nm. This peak is consistent with previously reported studies on iron nanoparticles synthesized via biological routes, indicating the successful reduction of ferric ions. The FTIR analysis further revealed the presence of functional groups such as alcohols, amines, and carboxylic acids, suggesting the involvement of phytoconstituents in the reduction and stabilization of nanoparticles. These biomolecules likely act as capping agents, enhancing nanoparticle stability and biological compatibility.

The XRD analysis confirmed the crystalline nature of the synthesized Fe_2O_3 NPs with an average particle size of approximately 136 nm. Although slightly larger than typical nanoscale materials, this size range still supports biological interaction and cellular uptake. The crystalline structure may contribute to improved reactivity and enhanced biological performance. The observed physicochemical characteristics collectively validate the successful synthesis of biofunctionalized iron nanoparticles using *Curcuma longa* extract.

The antidepressant activity of FeNPs was assessed using the Tail Suspension Test (TST) and Forced Swim Test (FST), which are widely accepted models for screening antidepressant agents. In both models, a significant reduction in immobility time was observed in FeNP-treated groups compared to the depression-induced group, indicating antidepressant-like activity. Notably, the higher dose of FeNPs (500 mg/kg) exhibited effects comparable to the standard drug imipramine, suggesting a dose-dependent pharmacological response.

The reduction in immobility time reflects decreased behavioral despair and improved stress coping mechanisms. These effects may be linked to the modulation of monoaminergic neurotransmission, particularly serotonin and dopamine pathways, which are known to play a crucial role in depression. Furthermore, the antioxidant properties of both iron nanoparticles and *Curcuma longa* phytoconstituents may contribute significantly to the observed effects. Oxidative stress is a well-established factor in the pathophysiology of depression, and its attenuation can lead to improved neuronal function and mood regulation.

Curcumin, the principal bioactive compound of *Curcuma longa*, has been extensively reported to exhibit neuroprotective, anti-inflammatory, and antidepressant properties. When used in nanoparticle synthesis, it may enhance the therapeutic potential of FeNPs through synergistic action. The phytochemical coating on nanoparticles may also facilitate better interaction with biological membranes and possibly improve penetration across the blood–brain barrier, thereby enhancing central nervous system activity.

Additionally, iron plays a vital role in brain function, including neurotransmitter synthesis and oxygen transport, which could further support antidepressant effects when delivered in nanoparticulate form.

Despite the promising findings, certain limitations should be considered. The study primarily focuses on behavioral models, and further investigations involving biochemical markers, neurotransmitter analysis, and molecular pathways are necessary to elucidate the exact mechanism of action. Additionally, long-term toxicity and safety studies are required before clinical translation.

Overall, the results of this study suggest that green synthesized iron nanoparticles using *Curcuma longa* extract possess significant antidepressant potential. The combined effects of nanotechnology and phytotherapy offer a novel and sustainable approach for the development of alternative treatments for depression. Future research should focus on mechanistic insights, optimization of dosage, and clinical evaluation to establish their therapeutic applicability.

5. Conclusion

The present study successfully demonstrated the green synthesis of iron nanoparticles (FeNPs) using *Curcuma longa* extract as an eco-friendly and sustainable approach. The phytochemicals present in the extract effectively acted as reducing and stabilizing agents, leading to the formation of biofunctionalized nanoparticles with desirable physicochemical properties. Characterization studies using UV–Visible spectroscopy, FTIR, and XRD confirmed the successful synthesis, stability, and crystalline nature of the FeNPs.

The synthesized nanoparticles exhibited significant antidepressant-like activity in both the Tail Suspension Test (TST) and Forced Swim Test (FST), as evidenced by a marked reduction in immobility time. The higher dose of FeNPs showed effects comparable to the standard antidepressant drug, indicating a dose-dependent response. These findings suggest that the observed pharmacological activity may be attributed to the combined antioxidant, neuroprotective, and anti-inflammatory properties of iron nanoparticles and *Curcuma longa* phytoconstituents.

Overall, the study highlights the potential of plant-mediated iron nanoparticles as a promising alternative strategy for the management of depression. The integration of nanotechnology with herbal medicine offers a novel therapeutic avenue that is both cost-effective and environmentally safe. However, further studies involving detailed mechanistic investigations, toxicity profiling, and clinical evaluation are essential to validate their safety and efficacy for human use.

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